NIEHS *Strategic Plan 2000*

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

A FIVE-YEAR PROGRAM: NEW OPPORTUNITIES IN ENVIRONMENTAL HEALTH RESEARCH

MARCH 2000

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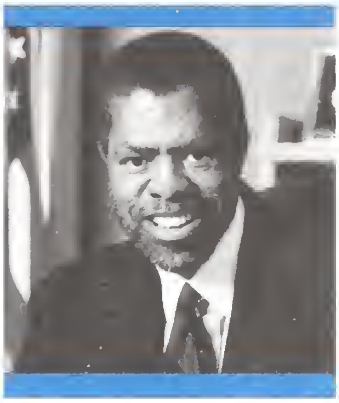


Steve McCaw. Image Associates

Kenneth Olden, Ph.D. — Director, National Institute of Environmental Sciences

LETTER FROM THE DIRECTOR

I am pleased to provide to you the Strategic Plan 2000 for the National Institute of Environmental Health Sciences (NIEHS). It represents our vision of where we want to move the field of environmental health sciences over the next five years. The core concepts that guide our planning and research efforts are that (1) it is better to prevent disease than to have to treat disease, and (2) controlling environmental exposures is one of our best disease prevention strategies.

The mission of the NIEHS is to reduce the burden of environmentally associated diseases by defining:

- how environmental exposures affect our health;
- how individuals differ in their susceptibility to these exposures; and
- how these susceptibilities change with age.

Fulfilling this mission requires that the NIEHS support the highest quality research and identify and pursue the opportunities created by new technologies. It also requires that we communicate with you, the American people, to explain our current research strategies and to hear what environmental problems are of concern to you. This communication between NIEHS and the public is accomplished in part by the regular Town Meetings we hold throughout the country at which many concerned citizens are heard. This Strategic Plan is another way to communicate and to get your input.

This document focuses on some of our new and expanded initiatives. The breadth of our research portfolio, however, prevents us from covering all of the research and training efforts we support. For a more detailed account of our research portfolio, please visit our web site at: **http://www.niehs.nih.gov/**

Kenneth Olden

Kenneth Olden, Ph.D.

Introduction

MISSION: ***Reduce the burden of environmentally-associated disease and dysfunction by defining (1) how environmental exposures affect our health, (2) how individuals differ in their susceptibility to these exposures, and (3) how these susceptibilities change over time.***

THE JOB OF NIEHS: PREVENTIVE MEDICINE

Preventing disease is one of the most important services a government agency can provide to citizens. Protecting people from avoidable illness and death saves money, spares suffering and improves the quality of life for society.

The most effective way to prevent disease and disability is to understand the cause of an illness and change the conditions that permit it to occur. A key strategy for preventing many diseases or minimizing disease progression is to minimize or eliminate adverse effects of chemicals in the environment and food supply. This preventive strategy underlies the concept of "environmental health." The premier research facility for this discipline in the U.S. is the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health (NIH).

The NIEHS pursues its goals by studying the impact on human health of a wide variety of chemical and biological agents found in the air, ground, food and water. Among the types of agents NIEHS studies are the following:

- industrial chemicals
- food and nutrients
- agricultural compounds
- infectious agents
- pharmaceuticals and medicinal herbs
- socioeconomic and lifestyle factors
- by-products of combustion and industrial processes
- physical agents such as heat and radiation

This information is acquired by laboratory and field testing done either by NIEHS or by research laboratories at academic centers that receive support from the institute; and it forms the backbone of many of the important regulations established by the Environmental Protection Agency, the Food and Drug Administration and other government oversight and regulatory agencies. This information is also the scientific basis for many laws passed by the U.S. Congress to protect the health of U.S. citizens.

The NIEHS is unique in the size and breadth of its mission. The Institute is headquartered in Research Triangle Park, North Carolina, where it conducts research

NIEHS *Retrospective*

A SAMPLING OF ACCOMPLISHMENTS

Isolated the first breast cancer susceptibility gene, BRCA1, in collaborations with scientists at the University of Utah Medical Center; this discovery enhances our ability to understand and treat inherited forms of breast cancer.

Steve McCaw, Image Associates

BRCA1 Team Leaders

Showed that calorie-restricted diets slowed the development of bladder cancer in mice by reducing levels of the hormone, insulin-like growth factor (IGF-1); this finding could lead to new preventive and treatment strategies for cancer.

Reported that dichlorvos, a commercial pesticide, causes leukemia and pancreatic and mammary gland tumors in laboratory animals; this finding lead to removal of dichlorvos-based pest strips and flea collars from the market.

Linked asbestos exposure to increased risk of cancers of the lung and lung lining, particularly in smokers; this finding lead to removal of asbestos insulation from the market, workplace, and schools.

through the Division of Intramural Research (DIR). The majority of NIEHS-supported research and training, however, is done through grants and contracts that are competitively awarded to university and independent laboratories throughout the country. The Division of Extramural Research and Training (DERT) oversees this larger part of the NIEHS enterprise. The Office of the Director (OD) and the Office of Management (OM) oversee and manage the efforts of the two divisions.

The NIEHS also supports university-based environmental research Centers. These Centers have a specific research focus, such as health effects of agricultural exposures or environmental components of childhood asthma, which engages the activities of a multidisciplinary group of scientists. In addition, each Center has a Community Outreach and Education Program (COEP) that serves specific environmental health needs of the locality in which it resides. The COEP ensures that Center scientists remain in touch with the real-world needs of their local citizens.

The NIEHS is unique within the National Institutes of Health because its primary focus is to prevent disease rather than to find ways to treat illnesses already afflicting people. The institute does this by approaching health as an integrated response of all organ systems of the body to the environment. Areas of special interest to NIEHS are cancer, birth defects, asthma, diabetes, infertility, neurodegenerative and developmental disorders and autoimmune disease. Thus, rather than focusing on one or two specific organs, like the heart or liver, the NIEHS takes a holistic approach to human health and a preventive approach to medicine.

This focus on preventive medicine reflects the findings of national surveys, which repeatedly find environmental health is one of the top priorities of the American public. Americans believe that reducing exposures to adverse environmental agents is the best way to protect their health and the health of their children. This belief is supported by a continually growing base of knowledge suggesting that environmental chemicals may be important triggers of many human medical problems, such as:

- cancer
- autoimmune diseases
- Parkinson's Disease
- neurodegenerative disorders
- birth defects
- asthma
- heart disease
- diabetes
- learning and behavioral disorders
- kidney disease
- infertility
- uterine fibroids
- osteoporosis
- low birthweight

A major component of NIEHS research investigates how exposures to specific agents, such as an agricultural compound or water contaminant, affect health. The institute conducts and supports such studies both in whole animals in the laboratory as well as by doing epidemiologic studies of the occurrence of the disease and relevant environmental exposures in humans. This work gives valuable insight into the potential of certain environmental agents to cause specific diseases or disabilities. In turn, this insight can lead to an improved understanding of the underlying mechanisms by which these agents act. These studies are further complemented by research that identifies early markers of exposure or disease, called biomarkers, that can potentially be used as early warning systems in clinical practice.

HOW NIEHS DOES ITS WORK: UNDERSTANDING THE HUMAN BODY IN HEALTH AND DISEASE

The substantial long-term commitment the U.S. has made to funding the basic sciences has lead to significant improvement in our understanding of the nature of disease at the cellular and molecular level; and it has provided researchers with extraordinary tools for unraveling the secrets of the genetic basis of disease and genetic susceptibility to disease-causing agents. NIEHS is using and extending this information to make further advances in the area of environmental health, especially in the understanding of the very early molecular events that begin the disease process. Thus, a large part of the NIEHS research is devoted to understanding the fundamental biological processes that maintain life and how environmental agents can adversely affect these processes and set the stage for disease and disability.

In essence, an important goal of NIEHS is to describe the first of what can be visualized as a three-stage disease process (Figure 1):

- ***Stage 1:*** Initial "trigger," or initiating event that can be environmental in origin.
- ***Stage 2:*** Progression of cellular and molecular events that are set in motion by the trigger.

- *Stage 3:* Clinical signs that lead to diagnosis and treatment of the disease.

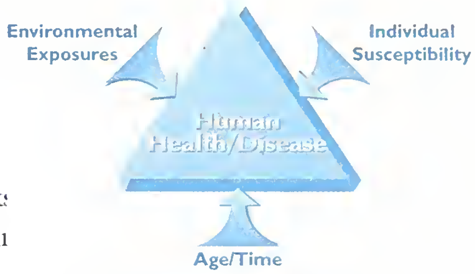
The key to prevention is successful intervention at Stage 1, before the disease process gets underway. However, as shown in Figure 1, much of biomedical research has concentrated on Stage 3, diagnosis and treatment. While more is now being learned about Stage 2 — the molecular and cellular events leading to disease — relatively little is known about Stage 1, the initiation of the cascade of cellular and molecular events that start the disease process. Yet this first stage is the most important one for successful disease prevention and intervention.

Further complicating our understanding of the environmental causes of disease is the fact that individuals can differ in their susceptibility to environmental agents. Some people can detoxify potentially dangerous compounds rapidly because their bodies have enzymes that break down these chemicals quickly. However other people's bodies may detoxify the same agents much more slowly. Consequently, they remain exposed to these potential dangers for a longer time.

Likewise, the ability of the body to repair environmental damage to genetic material varies from person to person. In addition, the level of toxicity of a particular environmental agent can vary depending on the time of life during which exposure occurred. For example, some agents may be particularly damaging during fetal development or infancy.

In sum, the following elements make up a person's "risk profile" for any potential environmental health hazard:

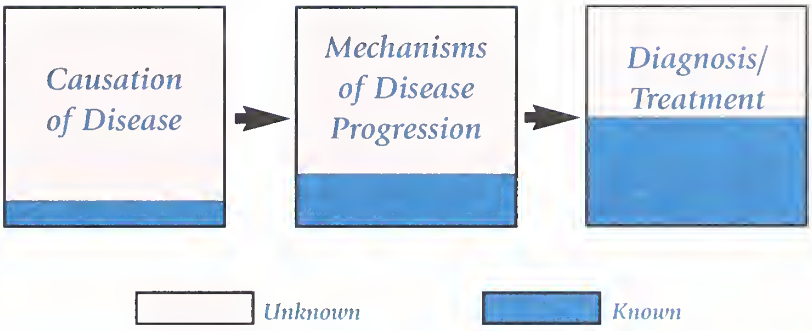
- Exposure to environmental agent
  such as chemicals and microorga
- Specific time at which exposures occur
- Underlying, individual susceptibility to these environmental agents



This complex interaction of risk factors and individual susceptibility increases or decreases the risk of disease in an individual, while obscuring the contribution of any specific one. However, new technologies and knowledge developed during the past several decades will help researchers tease apart these different elements as they relate to specific diseases.

Figure 1

INFORMATION AVAILABLE ON EACH STAGE OF DISEASE DEVELOPMENT



Understanding the nature of this differing susceptibility is especially important for enhancing our ability to identify environmental triggers of disease whose effect on health vary depending on the individual. Without such an understanding, an important source of disease could easily be obscured in studies that are not designed to account for individual levels of response. By defining the components of enhanced susceptibilities, the NIEHS enables risk managers to make decisions that protect our most vulnerable citizens.

In addition to contributing to the creation of new environmental health knowledge, the NIEHS also serves the public by empowering individuals and communities to manage, and reduce, their environmental problems. These programs include:

- Grants to support university-community partnerships that address local environmental health issues.
- Outreach activities required by NIEHS of academic research institutes it supports.
- Communication tools such as the *Report on Carcinogens*, the NIEHS journal *Environmental Health Perspectives*, and the public peer review of studies conducted under the auspices of the National Toxicology Program.

THE NATIONAL TOXICOLOGY PROGRAM

The NIEHS is also responsible for the leadership of the National Toxicology Program (NTP), a multi-agency organization that conducts toxicologic research on a broad array of public-nominated compounds. The NTP consists of relevant toxicology activities of the National Institutes of Health's National Institute of Environmental Health Sciences (NIH/NIEHS), the Centers for Disease Control and Prevention's National Institute for Occupational Safety and Health (CDC/ NIOSH), and the Food and Drug Administration's National Center for Toxicological Research (FDA/NCTR). The NIH's National Cancer Institute (NIH/ NCI) was a charter agency; however, the NCI Carcinogenesis Bioassay Program was transferred to the NIEHS in 1981. The NCI remains active in the Program through membership on the NTP Executive Committee.

NIEHS manages the process for setting research goals and priorities, oversees the conduct of research to assess the carcinogenicity and toxicity of environmental agents and develops new methodologies for toxicologic testing. Among its other duties, the NIEHS/NTP drafts the *Report on Carcinogens*, validates new test methods to reduce use of animals and convenes expert panels to evaluate the potential of specific chemicals to cause birth defects or reproductive problems.

NIEHS Strategic Plan Development Process

The NIEHS Strategic Plan 2000 reflects the Institute's mission to define how environmental exposures affect health, how individuals differ in their susceptibility to these exposures and how these susceptibilities change over time. In addition, the plan continues to support outreach programs that link the public directly with the strategic goals of NIEHS.

Each section of the plan includes a particular public health goal along with a description of the activity and a list of objectives that support the public health goal.

This strategic plan is the result of a multifaceted planning process that includes deliberations from annual leadership retreats, national town meetings, internal planning sessions focused on discrete research topics, and national conferences and workshops of subject-matter experts. This plan will be updated regularly with input both from scientists and the American public.

Some of the important new and expanded initiatives to be found in this document are:

- ***High-throughput Technology Initiative*** to develop new methods for carcinogenicity and toxicity testing that are quicker, cheaper and more reliable than current technologies;
- ***Sisters' Study*** that examines environmentally-associated risks of breast cancer;
- ***Children's Environmental Health and Disease Prevention Research Programs*** that focus on the unique vulnerabilities of childhood;
- ***Environmental Genome Project*** to identify genetic polymorphisms responsible for susceptibilities to environmental exposures, including the development of animal models of the various functional polymorphisms discovered by this project through the creation of Mouse Genomics Centers;
- ***Health Disparities Research*** to identify environmental components accounting for the poor health of the impoverished;
- ***Exposure Assessment Project*** to measure the real-world exposures to disease-causing agents that threaten people in the U.S.;
- ***Population-based Cohort Studies*** to more efficiently identify environmental components of human diseases;
- ***Complex Mixtures Studies*** to identify health effects from multiple, rather than single, exposures.

NIEHS Partnerships

BENEFITING THE AMERICAN PUBLIC AND THE AMERICAN TAXPAYER

The interdisciplinary nature of environmental problems requires a partnership of disciplines to solve them: epidemiology, toxicology, medical science and other specialties all have their own special contributions to make. NIEHS takes the lead in developing collaborations to enhance research and ensure that this work directly reflects the needs of the public. This powerful intellectual and technological synergy is the payoff to the public for its support of NIH in general and NIEHS in particular. This synergy ensures that the right people are tackling the right parts of any environmental health problem, while working in concert with other specialists to maximize the efforts of all for the benefit of society.

An example of this synergy is the Agricultural Health Study, a cooperative agreement between NIEHS and the National Cancer Institute. It was developed to identify which agricultural compounds pose a cancer risk to farmers. NIEHS recognized the benefit to providing extra funds to expand the scope of this study to include non-cancer risks as well as including the families of the farmers and pesticide applicators using these chemicals.

The benefits of this cooperation among various segments of NIH will accrue to a much broader segment of society, since the chemical exposures being studied — pesticides, solvents, nitrates, metals, mycotoxins, and silica — are not limited to rural settings. In addition, women's health endpoints can now be examined in this study, including premature ovarian failure, uterine fibroids, endometriosis, systemic lupus erythematosus (SLE) and menstrual function. The project also includes studies of the potential relationships between agricultural exposures and thyroid disease, Parkinson's Disease, diabetes, disorders of childhood growth and development, asthma and altered lung function, immune response disorders, degenerative eye diseases, and neurodegenerative and neurobehavioral diseases.

Among the other cooperative projects described in this report are partnerships with the following:

- ***Environmental Protection Agency*** to create a national network of programs on Children's Environmental Health and Disease Prevention Research;
- ***Department of Housing and Urban Development*** to survey American households for allergy-inducing (i.e., allergens) substances in their homes;
- ***Centers for Disease Control and Prevention*** to assess the levels of common endocrine-disrupting compounds to which the American public is exposed;
- ***Food and Drug Administration*** to develop a Phototoxicity Center that can assess how cosmetics, sun block additives, tanning enhancers, and skin colorants increase sensitivity to sunlight;
- ***International Life Sciences Institute*** to assess the usefulness of transgenic animals models for carcinogenicity testing;
- ***Pharmaceutical Industry*** to develop surrogate markers for safety.

ORGANIZATIONAL ACRONYMS USED IN THIS REPORT:

CDC	*Centers for Disease Control and Prevention*
DOE	*Department of Energy*
EPA	*Environmental Protection Agency*
FDA	*Food and Drug Administration*
HHS	*Department of Health and Human Services*
HUD	*Department of Housing and Urban Development*
ILSI	*International Life Sciences Institute*
NIOSH	*National Institute of Occupational Health and Safety*
NTP	*National Toxicology Program*
NIH	*National Institutes of Health*
• NCI	*National Cancer Institute*
• NEI	*National Eye Institute*
• NHGRI	*National Human Genome Research Institute*
• NHLBI	*National Heart, Lung, and Blood Institute*
• NIA	*National Institute of Aging*
• NIAID	*National Institute of Allergy and Infectious Diseases*
• NIAMS	*National Institute of Arthritis and Musculoskeletal and Skin Diseases*
• NICHD	*National Institute of Child Health and Human Development*
• NIDCR	*National Institute of Dental and Craniofacial Research*
• NIDCD	*National Institute of Deafness and Communication Disorders*
• NIDDK	*National Institute of Diabetes and Digestive and Kidney Diseases*
• NIEHS	*National Institute of Environmental Health Sciences*
• NINDS	*National Institute of Neurological Disorders and Stroke*
• NINR	*National Institute of Nursing Research*
• NIMH	*National Institute of Mental Health*
• ORMH	*Office of Research on Minority Health*
• ORWH	*Office of Research on Women's Health*

NIEHS Goals *and* Plans

OVERVIEW

The following pages describe in detail the nine functional goals the Institute has identified for the period 2000–2005. These goals are summarized as follows:

1. *GOOD SCIENCE FOR GOOD DECISIONS*

   Provide a sound, rational scientific foundation to support public environmental health policy.

2. *NEW TECHNOLOGIES*

   Develop the new technologies that will provide high-throughput, quick turnaround environmental health data in a way that is relevant and can be extrapolated to the human condition.

3. *ENVIRONMENTAL DATABASES AND REGISTRIES*

   Identify the environmental component of human diseases through strengthening existing databases and registries and creating new ones that track and monitor exposures and diseases.

4. *INDIVIDUAL SUSCEPTIBILITY*

   Define individual susceptibility to environmental exposures.

5. *ENVIRONMENTAL DISEASE COHORTS*

   Define the environmental and genetic components of many human diseases by establishing long-term, prospective studies.

6. *COMMUNITY NEEDS AND EMERGING HEALTH ISSUES*

   Ensure that the NIEHS and its research remains responsive to community needs and to newly emerging environmental health problems.

7. *CAREER DEVELOPMENT*

   Ensure a well-trained workforce in the environmental health sciences that reflects the diversity of the American people.

8. *COMMUNICATION*

   Enhance the understanding of environmental health sciences and its importance to human health among scientists, policy makers, and the American public.

9. *MANAGEMENT*

   Ensure responsible stewardship of the NIEHS research enterprise.

1.0 Good Science *for* Good Decisions

GOAL: ***Provide a sound, rational scientific foundation to support public environmental health policy.***

Public health policy is only as good as the science that supports it. The NIEHS has provided, through its own research and that done by NIEHS grantees, about 50 percent of the data used to set environmental standards and develop advisories to protect public health. The NIEHS pursues this goal by anticipating public health needs and using state-of-the-art science to create the new knowledge needed to fulfill those needs. The use of sound science to make accurate measurements in the laboratory and in the field ensures that the knowledge provided by NIEHS is accurate and relevant. Such knowledge, in turn, supports and justifies the formulation of thoughtful regulatory policies that protect human health without needlessly interfering with the nation's economic activity.

NEW OR EXPANDED OPPORTUNITIES

1.1 CHILDREN'S ENVIRONMENTAL HEALTH

Children are truly special. They are not small adults, but rather young, developing individuals whose physiologic makeup makes them potentially more vulnerable than adults to adverse environmental effects. Chemical exposures that have negligible effects in adults may have devastating effects in infants or children. This enhanced vulnerability of children is due to three factors:

- Organ systems in children are still developing, and thus are more susceptible to disruption and damage caused by environmental agents.
- Body mass in children is much smaller than in adults. Compared to an adult, a child consumes more food and water and breathes more air in proportion to his or her body mass. That means children generally get a bigger dose of whatever toxic agent is in contaminated food, water or air than do adults.
- Common early childhood behaviors such as crawling, putting objects into the mouth and ingesting dirt put infants and very young children in closer contact than adults with some toxic agents in the environment.

The consequences of childhood effects of environmental toxins can last a lifetime, which makes it imperative to have reduction of childhood exposures a critical component of environmental public policy. The NIEHS has traditionally played a pivotal role in shaping public policy in ways that protect the health of children; and the Institute continues to define how environmental exposures affect risks to diseases and disorders such as birth defects, neurological damage, cancers, and asthma. This information will inform policy makers of any changes that need to be made to safety standards to ensure the safety of children.

NIEHS *Retrospective*

CHILDREN AS A VULNERABLE POPULATION

On April 21, 1997, the White House released an Executive Order for the Protection of Children from Environmental Health Risks and Safety Risks. This Executive Order acknowledged the body of evidence, much of it obtained with support from the NIEHS, that showed children to be uniquely vulnerable to environmental health risks due to their smaller body mass and developing systems. This work includes the discovery that even low-lead levels can cause reduced intelligence and increased aggression in children, that polychlorinated biphenyls (PCBs) can lower intelligence of children exposed in utero, that children are more likely than adults to have breathing problems from air pollutants, and that early exposure to some pesticides can lead to neurological, reproductive, and immunological problems later in life.

Photo Courtesy of International Programme on Chemical Safety

Objectives:

- Establish a national network of Children's Environmental Health and Disease Prevention Research Programs in conjunction with EPA.
- Enhance and improve the publicly accessible database of all federally funded research on children's environmental health. This Children's Environmental Health and Safety Inventory of Research (CHEHSIR) is a searchable website done in partnership with EPA. It can be found at http://www.epa.gov/chehsir.
- Define the unique vulnerabilities of children to major environmental agents to which they are exposed from conception through early adolescence.
- Increase the pool of physicians with expertise in pediatric environmental medicine.
- Conduct clinical trials to evaluate the ability of Succimer to reduce or reverse neurological deficits arising from low-level lead exposures in children. (Succimer is used to treat acute lead poisoning, especially in small children. Succimer removes excess lead from the body by combining with lead in the bloodstream for removal by the kidneys.)
- Conduct trials to evaluate feasibility of household allergen reduction in preventing or ameliorating asthma in children (a partnership with NIAID).
- Evaluate, in rodents, the consequence of early exposures to pesticides on the neurologic, immune, and reproductive systems so that regulatory agencies can better address the issue of pesticide residues in food of infants and children.
- Determine if some cases of juvenile diabetes are associated with nitrate levels in drinking water (*see Agricultural Health Study*).
- Determine the environmental and genetic components of cleft palate birth defects (*see Cleft Palate Study*).

- Identify important environmental and genetic components of birth defects, childhood diseases and disabilities, and later adult diseases by following a cohort of infants from birth to adulthood (*see Birth Registries*).
- Continue studies of children in the Faroe Islands and Seychelles Islands to determine what, if any, long-term neurological or learning disabilities they sustain from exposures to methylmercury (Seychelles Islanders) or methylmercury/polychlorinated biphenyl mixtures (Faroe Islanders) that they ingest with their food. This information will be used by U.S. regulators to determine allowable levels of these pollutants in the air and diet of children in this country.

1.2 WOMEN'S HEALTH

Environmental agents likely play a role in a number of important diseases that are predominant in women, i.e., breast cancer, osteoporosis, ovarian dysfunction and ovarian cancer, uterine fibroids, and autoimmune diseases. The NIEHS approach has been to define the underlying genetic susceptibilities to these diseases, to investigate the role of estrogenic and other endocrine-active compounds (both natural and synthetic) in their etiology, to identify important environmental triggers for their development, and to explore the role of diet and nutrients in preventing or delaying these diseases. The new knowledge gained from these studies will help women better determine how to alter factors in their lifestyle that render them vulnerable to these diseases; and will help regulators better define standards that protect women from environmental triggers of these diseases.

Objectives:

- Identify the environmental and genetic components of breast cancer through lifetime cohort studies, including a large cohort of women whose sisters had breast cancer (*see Sisters' Study of Breast Cancer*).
- Define the ability of dietary supplements and therapeutic agents to prevent or delay breast cancer development, either alone or in combination, by conducting studies in mice genetically programmed to develop mammary tumors.
- Identify the environmental and genetic components of the autoimmune disease, systemic lupus erythomatosus (SLE), by following a cohort of people with this disease, the majority of whom are women.
- Define the relationship of uterine fibroids to race, hormonal status, diet, stress, and environment by conducting cross-sectional and longitudinal analyses of a cohort of women.
- Determine the ability of the micronutrient, boron, to prevent bone fractures from osteoporosis by conducting a clinical trial in an elderly population supplemented with boron.
- Evaluate the role of endocrine-disrupting compounds, both natural and synthetic, in the pathobiology of women's disease,

NIEHS *Retrospective*

ENVIRONMENTAL JUSTICE PROGRAM

Southeastern Los Angeles is an area in which heavy industry borders residential Hispanic neighborhoods. One such neighborhood was jolted by the discovery of a mountain of broken concrete and asphalt being created in its midst as part of clean-up efforts of earthquake-destroyed roads. The debris covered several acres and reached the height of a multi-storied building. Heavy dust was a constant reminder of the dump's presence. Concerned neighbors contacted a community group that was recently awarded an NIEHS Environmental Justice Research grant. This group was able to convince some city councilors to examine the site. One councilor had to leave the site when his lung collapsed and another when his asthmatic condition became aggravated by the dust. Although these two council members became supporters of a need to clean-up the site, the remaining majority members did not see a need for clean-up. The grantee, however, was able to broker a partnership with a nearby NIEHS Center to collect monitoring data and to use this information to convince the local air pollution agency to demand remediation. The debris and dust will be removed in 12 months and residents will be consulted at all stages of remediation. This same grantee engineered a smaller clean-up, this time of ground glass deposited in an outside storage area next to a residential neighborhood. This group used contacts with NIEHS-supported scientists to collect dust samples in the homes adjacent to this site and to show a high proportion of glass-containing dust and a higher-than-expected incidence of nose bleeds in children living in these homes. This information was instrumental in requiring the company to store its glass waste in a more responsible manner. These examples illustrate ways in which the NIEHS is using its resources to better serve the public, particularly the disadvantaged and minority populations which so often bear the greater burden of environmental hazards.

Photo Courtesy of Communities for a Better Environment

including cancers of the breast, uterus and ovaries, osteoporosis, uterine fibroids, endometriosis, and reproductive failures.

- Identify important environmental and genetic components of pregnancy complications such as preterm delivery and preeclampsia through following a group of women recruited during pregnancy (*see Birth Registries*).

1.3 HEALTH DISPARITIES AMONG DIFFERENT GROUPS

Major disparities exist between the health status norm in the U.S. and that of its socioeconomically disadvantaged groups, especially African-Americans, Hispanics/Latinos, American Indians, and Pacific Islanders. The most striking disparities include shorter life expectancy as well as higher rates of cancer, birth defects, infant mortality, asthma, diabetes, and cardiovascular disease.

Behavioral and lifestyle factors, nutrition and access to health care services (and quality of services rendered) are important contributors to this increased morbidity and mortality among socioeconomically disadvantaged populations. Nevertheless, environmental and occupational exposures, over which these individuals have little control, likely also play a prominent role. This disparity usually reflects the more hazardous living and working environments of individuals in the lower socioeconomic strata.

NIEHS has developed a number of research and outreach programs to address such health disparities, and is recognized as the leader in this endeavor. The research component improves our understanding of the environmental causes of health disparities. The outreach components, such as the Environmental Justice Grants and the Community-Based Prevention/Intervention Research grants, help empower disadvantaged communities with resources to effect healthful change.

In addition, there is increased awareness that these health disparities arise within a cultural context and that strategies for their resolution must be not only culturally appropriate but also culturally sensitive. These latter efforts, however, are hampered by a paucity of biomedical researchers with close ties to poor or minority communities. Thus the NIEHS is augmenting its research efforts with training programs to encourage students from groups most adversely affected by health disparities to pursue biomedical research careers. We expect that their participation in the biomedical enterprise will greatly enhance the design of future studies and the participation of disadvantaged communities in these studies.

In the aggregate these programs will give researchers a clearer understanding of the role of environmental factors in health disparities, improve the ability of affected communities to direct change, and increase the pool of minority scientists with both the understanding and credibility needed to design and implement studies that address these important problems.

Objectives:

- Identify important environmental underpinnings of health disparities (a partnership with NIA, NIAMS, NIMH and NIOSH).
- Investigate the role of common, disease-causing environmental agents linked to low birthweight and evaluate the effectiveness of intervention and remediation strategies to address low birthweight (a partnership with NINR, NIDCR and NICHD).
- Extend our knowledge of how aging, race, and ethnicity affect prostate cancer risk and prognosis (a partnership with NIA and NCI).
- Empower affected communities and grassroots organizations to address environmental aspects of health disparities through novel grant programs that can provide the necessary resources. Two

NIEHS *Retrospective*

AIR POLLUTION AND NEW REGULATORY STANDARDS

Air quality standards for two important pollutants, ozone and particulate matter, are being re-evaluated in light of epidemiologic and laboratory studies that span three decades of monitoring and research. This research demonstrated significant health problems even at air pollutant levels below the EPA standard. In one NIEHS-funded study, more than 8,000 individuals in six cities were monitored for 14–16 years. It was found that people exposed to higher levels of particulate air pollution suffered increased risk of death and shortened life spans. Another study found that children represented a particularly vulnerable population, showing moderate to severe changes in lung function at particulate levels that only slightly affected most of the population. A third study has shown that asthmatics are more sensitive to ozone levels, with a 40 percent greater risk of death on days with the highest pollution levels.

current approaches are the NIEHS Environmental Justice Grants and the NIEHS Community-Based Prevention/Intervention Research grants.

- Require that every NIEHS-supported Center have a Community Outreach and Education Program (COEP) that responds to local needs and environmental concerns, with particular emphasis on the health of disadvantaged populations and children. The success and relevance of the COEP will be an important factor during consideration of grant renewals.
- Increase the number of minority environmental health scientists.
- Enhance the infrastructure of minority-predominant institutions through novel "bridge" or partnership grants between minority-predominant colleges and universities and larger, more resource-rich universities.

1.4 ASTHMA

From 1982 to 1994, asthma prevalence increased in the general population by 61 percent; and it increased by 72 percent among young people under age 18. Overall, deaths from asthma increased by 40 percent throughout the 1980s. Moreover, asthma is not only a major public health problem, it is also a major health disparity problem because the disease is more common in poor, inner-city households. Identifying the relevant environmental triggers of asthma, and reducing or eliminating them, offers one of the most promising approaches for dealing with this public health menace.

Objectives:

- Identify major environmental triggers of asthma development (a partnership with NIAID).
- Identify environmental components, such as household allergens and outdoor air pollutants, that contribute to asthma attacks or that enhance the severity of symptoms.
- Define the molecular mechanisms responsible for environmental induction of airway sensitivity that is characteristic of asthma.
- Define the gene-environment interactions that are critical to asthma development.

- Evaluate intervention programs that reduce or eliminate known allergen sources, such as cockroaches and dust mites; and determine if these programs can significantly eliminate household allergens and can reduce the incidence and severity of asthma attacks (a partnership with NIAID).
- Evaluate prevention programs that identify children at high-risk for asthma development and determine if eliminating known allergens is effective in preventing asthma development in these currently non-symptomatic children.
- Survey a representative sample of American households for common indoor allergens (cockroach, dust mite, dog, cat, mouse, rat, fungus) and evaluate the need to reduce exposures to these common allergens (a partnership with HUD).

1.5 PARKINSON'S DISEASE AND OTHER NEURODEGENERATIVE DISORDERS

There is accumulating evidence that environmental "triggers" might be linked to the development of some neurodegenerative diseases. This assertion has been bolstered by evidence that the synthetic heroin contaminant, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP), elicits Parkinsonism. MPTP is structurally similar to some herbicides and pesticides. In fact, case-control studies have found an increased incidence of Parkinson's Disease associated with exposure to pesticides and herbicides, as well as to living in rural environments. Other studies have shown that consuming well water, living near industrial plants and working at printing plants or in quarries could also be associated with an increased risk of developing Parkinson's Disease. In addition, recent studies in twins show that, although genetic susceptibility plays a major role in early-onset Parkinson's Disease, it is a much less important factor in the more common, late-onset form. Thus some other factor, possibly environmental (and, thus, preventable), accounts for the majority of late-onset Parkinson's Disease cases.

In addition to Parkinson's Disease, environmental agents might play a role in Alzheimer's and amyotrophic lateral sclerosis, as well as other neurodegenerative disorders. These neurodegenerative diseases need to be understood in terms of the actual triggering event for disease initiation, the underlying genetic susceptibilities that make an individual more vulnerable to these triggers, and the mechanisms of disease progression.

Objectives:

- Identify the environmental components of Parkinson's Disease and other neurodegenerative disorders (a partnership with NINDS).
- Identify the stages of life at which a person is most vulnerable to disease initiation.
- Define the role of genetic susceptibility in enhancing disease-induction by environmental agents.

- Develop early biomarkers for environmentally-related disease (a partnership with NINDS).
- Develop animal models that can be used to study environmentally-induced neurodegenerative diseases.
- Increase the pool of physicians and scientists with expertise in environmental causes of Parkinson's Disease (a partnership with NINDS).

1.6 AUTOIMMUNE DISEASES

Autoimmune diseases are disorders in which an individual's immune system attacks the person's own tissues. An environmental component is suspected in the development of a number of autoimmune diseases, including scleroderma, multiple sclerosis, systemic lupus erythematosus, diabetes mellitus, and rheumatoid arthritis. The NIEHS, in collaboration with other entities within the NIH, as well as the EPA and private foundations, hosted a workshop on "Linking Environmental Agents and Autoimmune Diseases." This workshop assessed the current state of knowledge on the role of genetics and exposure to environmental agents and their interaction in initiating or exacerbating autoimmune diseases. In order to stimulate research on the role of environmental agents in autoimmune diseases, recommendations from this workshop were formulated into a Request for Applications (RFA) to be jointly sponsored by the NIEHS and other NIH components. In addition to this research, the NIEHS has established the Carolina Lupus Study that investigates environmental and genetic components of the autoimmune disease systemic lupus erythematosus (SLE).

Objectives:

- Identify and characterize environmental exposures (chemical, physical, or infectious) that singly or in combination initiate autoimmune diseases or exacerbate existing autoimmune disease (a partnership with NIA, NIDDK, NIAMS, NICHD, NIDCD, NEI, NHLBI, NIMH, NIDCR and ORWH).
- Identify critical exposure periods that increase susceptibility to autoimmune-inducing agents, such as fetal, perinatal, prepubertal, adult, or elderly.
- Identify genetic components that can increase susceptibility to autoimmune diseases.
- Identify the molecular mechanisms by which autoimmune-inducing agents elicit their response.
- Develop in vitro screening systems and animal models for evaluating environmental agents for their ability to elicit autoimmunity.

THERE IS LITTLE DATA DESCRIBING POSSIBLE ADVERSE HEALTH EFFECTS FROM HEAVY OR PROLONGED USE OF MEDICINAL HERBS.

1.7 HERBAL MEDICINE

Many of the herbal preparations on the market today may offer significant symptomatic relief or preventive actions; indeed, some of the best known and most valuable drugs (aspirin, digitalis, quinine) are of botanical origin. However, there is little data describing possible adverse health effects associated with heavy or prolonged use of medicinal herb formulations. In response to this lack of knowledge, the NTP, with the support of the NIH Office of Dietary Supplements, the Department of Health and Human Services' Office of Disease Prevention and Health Promotion, the FDA Office of Special Nutrition, and the Society for the Advancement of Women's Health Research, organized an international workshop that let experts identify the most relevant and obvious research needs on the safety and efficacy of medicinal herbs. Based on these recommendations, the NIEHS, under the auspices of the NTP, will conduct studies to fill knowledge gaps on the biological activity of popular herbal preparations. Selection of herbal products for study will be based on magnitude of use, presence of suspected or known toxicants in herbal products, and overall public health concern.

Objectives:

- Assess toxicity of common herbal preparations, particularly their ability to cause reproductive, neurological and immunological toxicity.
- Assess the health consequence of long-term, chronic use of common herbal preparations.
- Define potential herb/herb and herb/drug interactions, particularly in sensitive subpopulations.
- Identify the molecular basis of herbal efficacy and toxicity.

1.8 EXPOSURE ASSESSMENT PROJECT

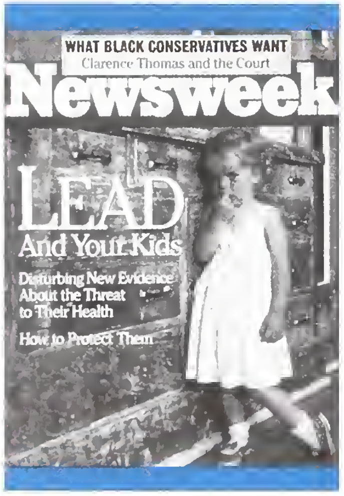
Little is known about the actual human exposure and body burden of chemicals we encounter in our environment. This knowledge gap hampers regulatory decision making and stymies attempts at setting testing priorities based on real-world exposures. It also limits our understanding of disease etiology and development of effective prevention and intervention strategies. In response to this need for more information, the NIEHS developed pilot programs with the CDC to measure levels of selected environmental toxicants or their metabolites in serum and/or urine from the general population of the U.S. A similar program operated in cooperation with the National Institute of Occupational Safety and Health evaluates complex mixture(s) of substances in occupational settings. A National Allergen Survey in homes across the country is being conducted in conjunction with the Department of Housing and Urban Development. The NIEHS continues to investigate other interagency partnerships to more fully develop this project in order to maximize its public health impact.

NIEHS *Retrospective*

GOOD SCIENCE FOR GOOD DECISIONS

The NIEHS has a long history of providing environmental health research that is used by regulatory agencies to enact laws to protect public health. Implementation of these laws on a national scale has resulted in many significant successes, including dramatic reduction of blood lead levels in children, improvements in air quality, and reductions in exposures to hazardous chemicals in the workplace.

Although these accomplishments are important on a national scale, environmental health problems are often local and frequently affect disadvantaged populations that are the least able to find ways to resolve these problems. Recognizing the need to extend its scientific capabilities to benefit local communities, the NIEHS established several novel programs. These include (1) the requirement that all NIEHS-supported Centers have a community outreach and education program (COEP) so that the scientific expertise at the Centers can be used to solve regional environmental health issues and educate local citizens, (2) Environmental Justice Grants to provide research into environmental health problems of the disadvantaged, and (3) the Community-Based Prevention/Intervention Research Program that provides resources and support to implement culturally-relevant prevention/intervention activities in disadvantaged or underserved populations. Collectively these programs broker partnerships between researchers and local communities to the benefit of both.


WHAT BLACK CONSERVATIVES WANT
Clarence Thomas and the Court
Newsweek
LEAD
And Your Kids
Disturbing New Evidence About the Threat to Their Health
How to Protect Them

Objectives:

- Analyze presence in general population of common, suspected environmental endocrine disruptors (partnership with CDC).
- Define the complex mixtures associated with environmental exposures in the paving, metal working, and cellulose installation industries. Evaluate the feasibility of replicating these mixtures in controlled laboratory settings and, if feasible, conduct rodent studies on the real-world exposures common in these industries (a partnership with NIOSH).
- Assess the presence of eight common allergens in households throughout the Nation (a partnership with HUD).
- Spearhead a national effort to strengthen information on exposures of the American public and foster federal partnerships to improve registries and databases.
- Investigate the feasibility of mapping environmental exposure levels by region and prevalence of diseases by region. These maps could indicate potential areas for study of exposure-disease relationships (a partnership with U.S. Geological Survey).

1.9 VALIDATION AND REGULATORY ACCEPTANCE OF NOVEL TEST METHODS

Investing in the development of improved methods for testing environmental agents and their effects will be futile if the accuracy and reproducibility of these results are not validated, or if the regulatory community does not approve them for use in official testing laboratories. Thus, NIEHS spearheaded formation of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). Already ICCVAM has evaluated and recommended two new test methods for regulatory acceptance, one using an in vitro system for evaluating skin corrosiveness of compounds and one using a lymph node assay in mice to assess the sensitizing abilities of chemicals. Both of these tests, which replace protocols that caused pain and suffering in animals, can now be used in submitting data to regulatory agencies.

To help accelerate ICCVAM's contributions, the NIEHS has established an NTP Interagency Center for the Evaluation of Alternative Toxicological Methods. This Center will provide the staffing necessary to convene workshops, meetings of experts and peer review panels for consensus development, and will broker public/private partnerships for developing and validating additional new tests.

Objectives:

- Evaluate a frog embryo assay designed to predict adverse effects of compounds on developing organisms.
- Assess the validity of a new acute oral toxicity test that uses only eight animals, rather than 100–200.
- Review the existing test methods that attempt to predict the endocrine-disrupting potential of environmental compounds.

1.10 COMPLEX MIXTURES

People are often exposed to environmental agents as components of a "cocktail" of different compounds, rather than as single agents. Yet laboratory studies and regulatory decisions are based on the effects of individual compounds because of the difficulty in studying compounds as part of mixtures. In order to make risk assessment more relevant, the NIEHS is spearheading efforts to develop techniques to study environmental agents as complex mixtures.

Objectives:

- Develop animal models, in vitro cell systems, and gene expression systems that can evaluate mixtures of chemicals.
- Define the molecular and cellular perturbations associated with exposure to both simple and complex mixtures.
- Investigate the effects of metal mixtures on molecular and cellular functions.
- Develop methods to characterize chemical mixtures in human populations and the environment.
- Develop statistical and mathematical risk assessment models that accommodate information generated on complex mixtures.

1.11 MOLECULAR BASIS FOR ENVIRONMENTALLY-INDUCED DISEASES

The toxic effect of an environmental agent is one of the several events that occur at the molecular or cellular level and leads to disease. The effect may manifest itself as genetic damage, disruption of routine signaling between cells and organ systems or interference with routine biological repair mechanisms in the body. Thus NIEHS devotes much of its research to understanding the fundamental biological processes that maintain life and how environmental agents can adversely affect these processes, thus setting the stage for disease and disability.

Understanding such molecular events has two benefits:

- Development of therapeutic strategies that intervene or prevent these diseases.
- Design of better animal models to study human disease and to extrapolate from results in animals to expected health effects in people.

For example, many liver carcinogens found in rodents also cause a significant increase in the numbers of small cellular bodies called peroxisomes. Although this is a common observation in rodents, there is no definitive evidence of how this phenomenon, called "peroxisome proliferation," relates to humans. This is necessary to determine whether findings from studies of carcinogens in rodents that cause peroxisome proliferation have relevance to human exposures. The issue is pivotal to regulatory control of many important compounds. For these reasons, the NIEHS has several projects devoted to understanding the molecular mechanisms underlying environmentally-induced diseases and disorders.

Objectives:

- Define the molecular events important to the normal and abnormal development of breast tissue to better define the stages at which environmental agents cause breast cancer.
- Define the cellular and molecular events that lead to chronic beryllium disease in order to improve the identification of markers of disease initiation and progression in order to design early intervention and environmental control strategies (a partnership with NHLBI, NIOSH and DOE).
- Define how environmental toxins cause cell injury and death and define the steps by which these events lead to neurodegenerative disease (a partnership with NINDS).
- Examine the mechanisms by which environmental exposure, individual susceptibility and age interact to cause Parkinson's Disease.
- Identify the mechanisms by which environmental agents and pathogens initiate or exacerbate autoimmune diseases.
- Identify the critical steps in early neurological development that can be adversely affected by environmental agents and lead to neurodevelopmental abnormalities such as learning and behavioral disorders. Critical molecular events include cell division, differentiation, cell adhesion, cell-cell communication, growth

HELPING COUPLES CONCEIVE

The desire to have children is a natural and profound basis for many human relationships. For some couples, however, conception proves to be difficult to achieve. Although structural anomalies account for some of these cases, events surrounding fertilization and implantation of an egg are also enormously sensitive to environmental influences, many of which are within a couple's control. NIEHS studies have uncovered a number of important environmental influences on female fertility, including (1) caffeine consumption, such as in colas and coffee, can reduce fertility, (2) exposure to nitrous oxide, the "laughing gas" used in dentists' offices, can reduce the likelihood of conception for female dental hygienists and dentists, who are exposed to high levels, (3) douching reduces a woman's chance to conceive, (4) cigarette smoking reduces a woman's probability to conceive, but these results are reversed when she stops smoking and (5) the ideal time for intercourse to lead to conception is earlier than previously thought, reaching an optimal time six days prior to ovulation. The NIEHS also examines environmental effects on male fertility. This work has led to the discovery that men taking calcium channel blockers for their hearts have fertility problems because calcium channels are important in sperm activation. Fortunately this effect is reversible when men stop taking the medication. These examples illustrate some of the simple changes couples can make to improve their chances of having children.

The findings on women's fertility would have been impossible without earlier work supported by the NIH to develop sensitive assays. One, an assay for human chorionic gonadotrophin (HCG), was first supported by the National Institute of Child Health and Human Development (NICHD).

factors, receptor activation, signal transduction and apoptosis.

- Explore the mechanisms by which peroxisome proliferation affects cancer induction and define the relevance of this mechanism to human cancers.
- Determine if environmental agents, through initiation of reactive oxygen species in the body, cause oxidative damage at the cellular level that translates into human diseases such as heart and lung disease.
- Define how environmental agents modulate or alter important cellular communication pathways such as growth factors and signal transduction, the effect of this alteration of normal cell growth and death, and whether or not such modulation leads to human diseases such as cancer.
- Define the molecular mechanisms by which the human body protects itself from environmental damage, such as through DNA repair enzymes and detoxifying enzymes, and how impairment of these processes leads to human disease.
- Investigate how environmental agents can alter imprinted gene expression, causing epigenetic changes in DNA that result in a variety of genetic diseases such as cancer and behavioral and developmental disorders.

2.0 New Technologies

GOAL: ***Develop the new technologies that will provide high-throughput, quick turn around environmental health data in a way that is relevant and can be extrapolated to the human condition.***

"Risk assessment" is an attempt to determine "how much is too much" of an exposure to a potentially harmful environmental agent. In order to calculate such a level — or range of levels — scientists must study epidemiological findings in human populations or generate laboratory findings on the effects of that agent in animals or cells. Using various mathematical tools, the scientists extrapolate what is known about the agent's effect into standards for exposure levels that fall well enough below that considered to be harmful based on these initial studies. The technique of risk assessment is not straightforward; rather, it can be difficult and may require making certain assumptions based on available data.

Current risk assessment methodology uses results of bioassays in rodents exposed at high doses and extrapolates this information to probable health effects in humans exposed to much lower doses. This methodology, although the best currently available, is slow in generating information, must employ arbitrary assumptions and safety factors to account for the numerous unknowns in extrapolating rodent data to human conditions, and cannot accommodate much of the data being generated by new molecular biological techniques, such as the effect of genetic polymorphisms on response. The NIEHS seeks to improve the science of risk assessment by developing:

- Screening models that are quicker and more relevant to humans.
- Methodologies that combine exposure data, toxicology, mechanistic data and genetic susceptibility.

The application of these new technologies is not limited to risk assessment. They might also have applications in the pharmaceutical industry, where there is a need to rapidly assess the toxicity of candidate drugs. These technologies can also be used to develop novel transgenic animal models that improve our understanding of environmental links to important human diseases.

NEW OR EXPANDED OPPORTUNITIES

2.1 HIGH-THROUGHPUT TECHNOLOGY

An enormous number of chemicals are commonly used in high volumes by various industries yet many of these chemicals have not been assessed for their potential to harm humans. Not all may require testing, since they are very similar to chemicals that have already been studied. However, several do need more testing. Yet, using current technologies researchers will never be able to keep up with the demand for testing these chemicals and new ones that are developed.

For the past 40 years, the accepted method for identifying carcinogens has been the rodent bioassay. These assays cost two to six million dollars per chemical and take five to seven years to complete. But by exploiting recent advances in human genetics and recombinant DNA technology, researchers can develop animal models and in vitro assay systems to identify carcinogens and toxicants in a matter of weeks rather than years. This alternative both saves money and reduces the number of animals used. For example, DNA microarray technology may allow toxicologists to expose cells or tissues to chemicals whose toxicity is unknown, and match the results against the "signature," or common set of changes in gene expression, produced by a known class of toxicants. This would reduce the need for lengthy and expensive rodent bioassays and could lend itself to testing for the effects of both low-dose exposure and long-term exposure. Thus, the use of DNA microarray technology to assess changes in gene expression in response to specific environmental exposures is a rapidly growing research area that could have a large impact on the environmental health sciences. The NIEHS is leading the development and validation of this new application to environmental health science, which could revolutionize the field of risk assessment.

Also, it is now possible to modify in animal models those genes that are involved in orchestrating the carcinogenic process. For example, incorporating a chemical-inducible oncogene into the germline produces animals with multiple copies of this oncogene in all the cells of the organism. Conversely, it is possible to delete one copy of a tumor suppressor gene. Such so-called transgenic animals are much more responsive to carcinogenic exposures.

Preliminary studies showed that tests using these animals identified carcinogens in months rather years. NIEHS has taken the lead in establishing a major collaborative effort including the EPA, the FDA, the pharmaceutical and chemical manufacturing industry, and two foreign governments (Japan and the Netherlands) to validate the four transgenic mouse models currently available for their capacity to predict carcinogenicity.

Structural biology is also having a great impact on environmental health research. Over a decade of NIEHS-supported research recently culminated in the ability to present three-dimensional models of molecules with which scientists can assess the similarity, or homology, between different metabolizing enzymes. These enzymes are critical in biological systems that convert ingested harmful environmental substances into less toxic, easily excretable compounds. Understanding how similar, or different, these critical enzymes are in different species is key to extrapolating toxicology results in rodents to humans. These structure-activity studies represent substantial progress toward rationalizing and predicting individual, strain and species differences in toxin metabolism. In turn, it may be possible to link such findings to

Steve McCaw, Image Associates

ADVANCES IN COMPUTER TECHNOLOGY AND MOLECULAR BIOLOGY GIVE SCIENTISTS NEW TOOLS FOR STUDYING EXPOSURE-RESPONSE RELATIONSHIPS.

individual differences in susceptibility to toxins. Furthermore, knowledge of the structural basis of metabolizing enzyme specificity may lead to the rational design of inhibitors that modulate this metabolism and provide medical science with a way to block an important step in the development of cancer.

Objectives:

- Evaluate transgenic mouse models for their ability to more quickly assess chemical carcinogenesis, to do it with fewer animals, and to produce information that is at least as relevant to people as are current methodologies or, preferably, more relevant (a partnership with EPA, FDA, pharmaceutical and chemical manufacturing industry, and health agencies in Japan and the Netherlands).
- Evaluate the NIEHS-developed ToxChip that, using microarray technologies, can assess the ability of single chemicals and of chemical mixtures to initiate expression of thousands of environmental-response genes. Employ partnerships and collaborations with industry, federal and academic laboratories to establish proof of principle for this approach.
- Establish the structural basis of important toxicant-response proteins and evaluate the differences and similarities in the structure of these proteins across species.

2.2 COMPUTATIONAL BIOLOGY

The last ten years has seen revolutionary development of new knowledge and techniques in the fields of computer technology and molecular biology. The NIEHS and NTP are capitalizing on these advances to develop a better scientific basis for risk estimation from exposure to environmental compounds. The goal is to marry our understanding of the actual molecular mechanisms of disease development and toxicant effects with mathematical models generated by computers. These mathematical models will enable scientists to use structure-activity relationships, in vitro assays, and a limited amount of animal-based toxicology data to further elucidate how environmental agents alter critical biological systems and cause disease. These innovative models allow for a greater use of a broad spectrum of information, ranging from epidemiological findings to changes in the structure of genes and proteins. These models will also provide alternatives to animals for toxicity evaluation, and provide a sound, testable basis for low-exposure effects of environmental hazards. The regulatory community has already used several examples of this approach as a basis for improving risk assessments.

Objective:

- Develop biologically-based, computerized techniques that can merge into risk assessment deliberations all chemical, kinetic, and biological information available on an environmental agent.

2.3 SURROGATE MARKERS OF SAFETY

The pharmaceutical industry is using the powerful tools of molecular biology to develop large numbers of promising therapeutic agents. Unfortunately the large number of candidate drugs being produced greatly outstrips the industry's ability to assess these potential therapeutics for safety and efficacy. This shortfall in toxicologic assessment is creating a bottleneck that slows getting innovative drugs to the American people. The NIEHS is now leading an initiative to address this problem by developing and validating surrogate markers for clinical efficacy and safety that would quickly detect adverse drug effects early in the drug development process. If successful, this program will let pharmaceutical companies quickly and inexpensively screen the wide array of promising compounds to identify those that are both the safest and most efficacious. This program will also enhance the safety of human subjects in preliminary studies and clinical trials.

Objective:

- Develop surrogate markers for clinical efficacy and safety of new drugs that will be a more effective screen early in the drug development process than are current model systems.

2.4 MOUSE GENOMICS CENTERS

The genetic makeup of an individual person is a major factor in susceptibility to environmentally-related human disease. Furthermore, specific genetic variations, called polymorphisms, may contribute to either resistance or susceptibility to environmentally-induced diseases. It is essential to understand the biological significance of these genetic polymorphisms in order to better predict health risks and develop environmental policies that protect the most susceptible people. Therefore, NIEHS will support the development of new resource centers that use all available DNA sequence variation data to produce novel transgenic and knockout mouse models that mirror specific polymorphic variants of human environmental response genes (ERG) found in the general population. These ERG include those genes that:

- Control distribution and metabolism of toxins;
- Operate DNA repair pathways;
- Control the cell cycle;
- Control cell differentiation and programmed cell death (apoptosis);
- Operate transduction systems for the expression of ERG.

This NIEHS initiative will establish cross-disciplinary, multi-institutional Comparative Mouse Genomics Centers whose component teams of investigators will:

- Develop or refine mouse models of environmentally-relevant human diseases.
- Provide a comprehensive analysis of mouse model phenotypes and genotypes.
- Validate model usefulness for a variety of investigations.

The novel models produced by the Centers will then be used by the scientific community to study disease sequelae of specific toxic exposures, including environmental agents, viruses, nutritional factors, pharmacological drugs, and other physical and chemical stressors.

Objectives:

- Perform comparative alignment of human-mouse sequence analyses.
- Develop cloning-sequencing-vector construction strategies.
- Produce transgenic and knockout animals and maintain breeding colonies of these animals.
- Develop, characterize, maintain and distribute mouse embryonic stem cell lines.
- Identify mouse lines suitable for tissue-specific and inducible mutagenesis.
- Validate the Cre-Lox system and other novel approaches for targeted mutagenesis.
- Develop and distribute relevant databases and other materials to enable investigators to use products of the Mouse Genomics Centers to study environmentally-associated diseases.

3.0 Environmental Databases *and* Registries

GOAL: ***Identify the environmental component of human diseases through strengthening existing databases and registries and creating new ones that track and monitor exposures and diseases.***

NEW OR EXPANDED OPPORTUNITIES

3.1 NATIONAL TWIN REGISTRY

The development of disease has both genetic and environmental components. The components are generally complexly tangled, obscuring their relative contribution to individual diseases. One of the most useful techniques for solving such a puzzle is by doing twin studies that compare the similarity of identical, or monozygotic (MZ), and fraternal, or dizygotic (DZ) twins.

Because identical twins share all their genes, whereas fraternal twins share, on average, only one half of their segregating genes, comparison of disease incidence or other similarities between these groups lets researchers assess the relative importance of genes and environment. Rates of addition of twins to the population are fairly constant: identical twins occur in about 4 per 1000 conceptions, regardless of maternal age or ethnicity. Fraternal twins occur in about 16/1000 conceptions in black Africans, 8/1000 in Europeans, and 2/1000 in Japanese or Chinese; rates of fraternal twinning increase with increasing maternal age.

A number of studies have already shown the value of such comparison. For example, autism, attention deficit/hyperactivity disorder and multiple sclerosis occur more frequently in identical twins than in fraternal twins, suggesting a genetic component to these disorders. In the case of late-onset Parkinson's Disease, however, there is no difference in rates between identical and fraternal twins, suggesting that environmental, rather than genetic, components may play a major role in this disease.

Currently, there are useful registries in Scandinavia, the Netherlands, Australia and the U.S. The U.S. registries include the mid-Atlantic states (Mid-Atlantic Twin Registry [MATR]); Missouri (focused on young adult women); Minnesota (focused on twins reared apart); Pennsylvania; a national registry of twins in the armed services during Vietnam war; the National Academy of Sciences/ National Research Council World War II Veteran Twin Registry; and others. The largest registry is MATR, which accrues about 3000 pairs per year, totaling about 500,000 people in VA, NC, SC and MD. In the entire U.S., it is estimated that there are about 5.6 million individuals belonging to a twin pair. The number of triplets and higher order identical siblings is due in part to increasing use of fertility enhancing drugs and in vitro fertilization technologies. The NIEHS is investigating ways to establish a National Twin Registry.

KNOWING HOW DISEASE RISKS COMPARE AMONG FRATERNAL AND IDENTICAL TWINS CAN GIVE IMPORTANT CLUES TO THE RELATIVE CONTRIBUTION OF GENETIC AND ENVIRONMENTAL FACTORS IN DISEASE DEVELOPMENT.

Such a registry would be a powerful tool for researchers and would also increase the power of the Human Genome Project.

Objective:

- Establish a National Twin Registry to evaluate the relative importance of genetic and environmental factors in major disease conditions (anticipated to be a trans-NIH partnership).

3.2 BIRTH REGISTRIES

Studies aimed at determining the adverse effects of low-dose exposures during fetal development are significantly complicated by the fact that many of these effects do not appear until much later in life. The best way to detect these prenatal effects in humans is through long-term epidemiologic studies that follow a child through the mother's pregnancy and into the later year's of a child's life. The NIEHS is pursuing such a collaboration with the Norwegian Government, which has an excellent infrastructure for this type of study, and is investigating ways to establish such a registry in this country.

The Norwegian government plans to establish a registry of 100,000 pregnant women and their children, beginning in 2000. Researchers will conduct a lifetime health assessment of individuals in this registry. NIEHS plans to support the collection and storage of biological samples (blood and urine) during the mothers' pregnancy. These samples could be used later to measure maternal and fetal exposure to environmental agents such as pesticides, plasticizers, and heavy metals. Questionnaires will be administered periodically throughout the mothers' pregnancy and the babies' childhood. Study participants will also be followed through the various Norwegian national medical registries. Important health outcomes include birth defects, preterm delivery, preeclampsia, childhood development, diseases of childhood and diseases of adulthood.

Objectives:

- Collect and store blood and urine of 100,000 pregnant women recruited by the Norwegian government (a partnership with the Norwegian government).
- Evaluate the stored samples for environmental toxicants and cross-reference this information with risks of birth defects, preterm delivery, preeclampsia, childhood development, diseases of childhood and diseases of adulthood (a partnership with the Norwegian government).
- Evaluate gene-environment interactions for diseases that are identified within this registry.
- Spearhead a movement to establish a U.S. Birth Registry (envisioned to be a trans-NIH and trans-government partnership).

4.0 Individual Susceptibility

GOAL: ***Define individual susceptibility to environmental exposures.***

There is wide variation in individual responses to environmental agents. This variation is accounted for by:

- Differences in environmental response proteins, such as those controlling metabolic capacity;
- Differences in DNA repair capacity;
- Co-existing diseases or infections;
- Differences in gender;
- Differences in nutritional status.

This large diversity in responsiveness among individuals to environmental toxicants makes it difficult to determine actual risks, particularly at the low doses to which most people are exposed. Opportunities now exist for studies of genetic susceptibility for cancer and other diseases in which an environmental component can be presumed. Knowledge from such studies could, in the future, allow markers of genetic susceptibility to be incorporated into epidemiologic studies. This, in turn, would permit adjustment of interpretation of results to account for genetic susceptibility, thus greatly enhancing the sensitivity and power of these studies to detect environmental components of important diseases. Other projects being considered are a nutrition initiative to determine how nutritional status alters disease susceptibility, and development of transgenic mice that carry important environmental response genes.

NEW OR EXPANDED OPPORTUNITIES

4.1 ENVIRONMENTAL GENOME PROJECT

The maintenance of health and the development of disease are determined by the complex interplay between genetic susceptibility, environmental exposures and aging. The rapid advances in molecular genetic technologies provide new opportunities to understand the genetic basis for individual differences in susceptibility to environmental exposure. The NIEHS is expanding its research program on genetic susceptibility to environmentally-associated diseases through a new Environmental Genome Project (EGP). This project will use technology developed by the Human Genome Project to identify genetic variants (polymorphisms) of environmental disease susceptibility genes in the U.S. population. By identifying those genetic variants that affect individual response to environmental agents, scientists can better predict health risks and assist regulatory agencies in the development of environmental protection policies.

While many genes that play a role in susceptibility to environmental exposure have been identified, the polymorphisms of these genes have not been systematically sought, identified, or reported. The goal of the Environmental Genome Project is to identify polymorphisms that confer altered sensitivity or resistance to specific environmental factors. The Project's ultimate aim is to provide markers of genetic susceptibility that, when, incorporated into epidemiologic studies, greatly enhance the ability of researchers to identify the environmental components of human disease.

The NIEHS Environmental Genome Project is a multi-disciplinary, collaborative effort, involving several other NIH institutes as well as the Department of Energy (DOE) and other federal agencies. Examples of categories that include environmental response genes are those that control or affect:

- Xenobiotic metabolism and detoxification;
- Hormone metabolism;
- Receptor-ligand interaction;
- DNA repair;
- Cell cycles;
- Cell death;
- Immune and inflammatory responses;
- Nutritional factors;
- Oxidative processes;
- Signal transduction systems.

The Project will make available a central database of the polymorphisms to support both functional studies of alleles and population-based studies of disease risk. Population-based epidemiological studies are central to the identification of both the genetic alleles and the environmental exposures that cause disease, and represent an integral component of the Environmental Genome Project. The Project will include additional susceptibility genes as they are discovered.

Objectives:

- Identify the genetic variants of environmental response genes that are relevant to enhanced or reduced susceptibility (i.e., have a functional significance) to toxins, beginning with single nucleotide polymorphisms (SNPs).
- Identify and characterize the functional significance of polymorphisms in environmental response genes that are also implicated in individual susceptibility to aging (a partnership with NIA).
- Define the mechanisms of genetic susceptibility to tobacco-induced cancers (a partnership with NCI).
- Provide EGP-generated information to researchers as quickly as possible by supporting a website, GeneSNPS, that integrates sequencing information on genes of interest as it becomes available.
- Ensure the ethical integrity of the EGP by ongoing evaluation of the ethics of the project and the information generated.
- Define the role of environmental response genes in the development of prostate cancer (a partnership with NCI and NIDDK).

4.2 GENDER-RELATED DIFFERENCES IN SUSCEPTIBILITY

Men and women are prone to unique gender-based health problems. For example, women appear to be at higher risk for autoimmune diseases, develop heart disease

MEN AND WOMEN CAN DIFFER IN THEIR RESPONSE TO ENVIRONMENTAL AGENTS.

at a later stage of life than men, but do not have as good a prognosis as men undergoing the same heart surgeries. We need to define the basic genetic and physiologic differences between men and women that account for variation in disease risk. Of particular concern is the role of chemicals in the environment that possess estrogenic or endocrine-disrupting activity and their possible contribution to an increased incidence of various diseases in hormone target tissue. There is some evidence supporting the hypothesis that those endocrine-active compounds, especially those that bioaccumulate, are related to increases in breast cancer, endometriosis, and uterine fibroids in women and, in men, decreased sperm count and quality, and reproductive tract abnormalities.

There are several promising lines of investigation that may help account for these gender differences. These include the difference in the hormonal milieu of males and females, differences in interactions among the neurological, endocrine, and immune systems, and differences in metabolic pathways and capacities.

Objectives:

- Define how estrogenic compounds affect homeostatic conditions in tissues such as bone, liver, circulatory, ovarian, uterine, and mammary tissues. The recent development of mouse models with estrogen receptor deficiencies [α-ERKO and β-ERKO] could be used to help define important estrogenic pathways and roles in both males and females.
- Define how environmental endocrine-disrupting compounds interfere with biological processes in males and females and how health endpoints differ by gender.
- Define differences in neurological, endocrine, and immune systems between males and females, how these differences change with life stage such as puberty or pregnancy, and how these differences alter susceptibility to environmental triggers of diseases such as thyroid autoimmune disease, systemic lupus erythematosus, and scleroderma.
- Define how men and women differ in their ability to metabolize and detoxify common environmental agents.
- Investigate if early fetal exposures account for some of the variation in disease risk seen between men and women.
- Continue the NTP protocol in which routine toxicologic testing is done in both sexes of rodents so that gender differences in toxicant responsiveness can be identified and the basic mechanisms for these differences can be studied.
- Develop biomarkers of susceptibility that could be incorporated into future studies.
- Develop a list of gender-related workplace exposures that can be used to guide future testing (a partnership with NIOSH).

NUTRITION CAN HAVE AN IMPORTANT BEARING IN DISEASE RISKS, INCLUDING A PERSON'S SUSCEPTIBILITY TO ENVIRONMENTAL AGENTS.

4.3 ANIMAL MODELS OF DISEASE SUSCEPTIBILITY

The study of many important human diseases, including the molecular basis of their pathology, has been hampered by lack of relevant laboratory models that duplicate these diseases. Recently developed techniques for introducing human genes into animals (transgenic models) or that eliminate a gene (knockout models) offer powerful tools for assessing how a genetic variant enhances disease susceptibility or how the lack of a particular gene affects disease onset. The NIEHS is evaluating current animal models for their relevance in understanding environmentally-induced diseases and creating new models that can help define the role of environmental agents in disease initiation and progression.

Objectives:

- Evaluate transgenic and knockout animals models to assess the chemopreventive effects of nutrients and therapeutics in breast cancer development.
- Use estrogen-receptor knockout mice to evaluate the probable effects of environmental endocrine disruptors, which may interact with these receptors to cause reproductive tract cancers, infertility, uterine fibroids and other diseases.
- Develop mouse models for the breast cancer susceptibility genes, BRCA1 and BRCA2.

4.4 NUTRITION INITIATIVE

Diet can play a strong role in individual susceptibility to environmental agents. For example, calcium can compete with charged metals such as lead for uptake in the body. Thus people with high-calcium diets absorb less lead from their environment than do those on low-calcium diets. Diet also affects cancer risk. People on low-protein diets have a reduced risk of aflatoxin-induced liver cancer than do those on higher-protein diets. Evidence also suggests that dietary phytoestrogens might reduce risks of sex hormone-related diseases such as breast cancer, prostate cancer, and osteoporosis. Maternal dietary deficiency in folate, an important micronutrient, has been linked with increased risk of neural tube defect in newborns.

In fact, it has been suggested that deficiencies of micronutrients such as folate could cause genetic instability, which would have significant implications in terms of risks from environmental exposures. For these reasons, the NIEHS is studying nutritional components of disease risks and is planning a Nutrition Initiative to enhance this work. The initiative will improve understanding of the molecular basis of nutrition while studying nutrients in the context of complex mixtures. It will also address the risks and benefits of high supplementation levels, particularly in the area of those antioxidants that may become pro-oxidants at high levels. This Initiative will also be used to develop communication and future collaborations between environmental health scientists and nutritionists.

Objectives:

- Convene a national workshop to evaluate research needs in nutrition and implement recommendations.
- Evaluate (1) the effect of both high and low levels of antioxidants on oxidative stress and free radical formation; (2) the effect of high-calorie or high-protein diet on cancer and other chronic diseases; and (3) the effect of phytoestrogens on breast and prostate cancers as well as risk of osteoporosis.
- Determine the best ways to study nutritional elements as complex mixtures.
- Assess the health consequences of depletion of critical micronutrients in the diet.
- Develop cost-effective ways to include diet parameters in existing epidemiologic studies.
- Improve collaboration between nutritionists and environmental health researchers.

5.0 Environmental Disease Cohorts

GOAL: ***Define the environmental and genetic components of many human diseases by establishing long-term, prospective studies.***

Prospective studies, where a large cohort of people are followed over many years and their health status is regularly monitored, have proved to be a rich source for understanding the importance of lifestyle factors in health. The same could hold true for assessing the importance of environmental exposures, as well as gene-environment interactions. Unfortunately, prospective studies that require recruiting large numbers of people are very expensive and are a long-term investment. To reduce its costs the NIEHS has developed new approaches and has created partnerships with a number of organizations to establish large cohorts that will yield insights about the health consequences of environmental exposures.

CLEFT PALATE IS A COMMON BIRTH DEFECT FOR WHICH NIEHS IS INVESTIGATING GENETIC AND ENVIRONMENTAL CAUSES.

Mary Rose Tully

NEW AND EXPANDED OPPORTUNITIES

5.1 CLEFT PALATE STUDY

Cleft lip and palate is a common, disfiguring birth defect. This condition is obvious at birth and results from miscues during fetal development of facial structures. The miscues may be triggered in the fetus by the mother's exposure to environmental toxins and interactions of these toxins with polymorphisms within the mother or fetus that make the baby more susceptible. To examine this hypothesis, NIEHS researchers are conducting a large study in Norway, which has one of the highest reported rates of facial clefts in the world; Norway also has a highly organized birth registry that records these defects. For this study, both genetic samples and data on environmental exposure of mothers and infants are being collected. Due to be completed in 2001, this study will provide the largest and most complete collection of data ever obtained on the genetic and environmental components of this birth defect.

Objective:

- Determine the genetic and environmental components of cleft palate birth defects.

5.2 AGRICULTURAL HEALTH STUDY

The Agricultural Health Study (AHS) is a large epidemiological study originally conceived by the NCI to examine how agricultural exposures affect cancer risks in farmers. The NIEHS developed a partnership with the NCI to expand this study to the spouses and children of farmers, to add non-cancer health endpoints to the study, and to increase the number of minorities recruited into the study. The benefits of this study extend beyond farmers because the exposures under study — pesticides, solvents, nitrates, metals, mycotoxins, and silica — are not limited to farmers but are common to rural communities and other settings.

Objectives:

- Identify cases of juvenile diabetes in this cohort to determine the relationship of this disease to nitrates in well water, as well as other agricultural exposures.

- Identify cases of Parkinson's Disease in this cohort and identify relevant exposures in its development.
- Identify cases of autoimmune diseases in this cohort and identify relevant exposures in its development.
- Identify cases of macular degeneration in this cohort and identify relevant exposures in its development.
- Identify cases of early ovarian failure (premature menopause) in this cohort and identify relevant exposures in its development.
- Examine gene-environment interactions of the above diseases, if sufficient cases are available within the cohort.

5.3 SISTERS' STUDY OF BREAST CANCER

Because women whose sisters had breast cancer are at increased risk of breast cancer themselves, the NIEHS plans to establish a cohort of 50,000 of these women, among whom twice as many breast cancer cases are expected than in any other cohort of similar size; approximately 500 cases are expected after five years. NIEHS will collect and store biologic specimens prior to disease onset and participants will regularly complete extensive questionnaires.

Breast cancer risk could be assessed in terms of exposure to endogenous hormones, exogenous hormone disruptors, growth factors, dietary components, and environmental contaminants such as pesticides and solvents. This study would also assess the importance of gene-environment interactions by studying polymorphisms of genes involved in metabolic activation, receptor binding, DNA repair, or detoxification. Although the effort would target breast cancer, less common, hormonally-related cancers such as ovarian and endometrial cancer could also be studied. Additionally as more breast cancer-related genes and exposures are identified, the databank could be regularly re-evaluated to address this new information. This study group might also be used to evaluate other exposures important for female-predominant diseases, such as autoimmune diseases, if a large enough subset of the cohort was identified as suffering from these conditions. A companion study will assess environmental risk factors by comparing incident breast cancer cases and their cancer-free sister and will explore similarities or differences in tumor characteristics between affected sisters.

Objectives:

- Define gene-environment interactions important to breast cancer development.
- Define gene-environment interactions in ovarian and endometrial cancers, if enough cases arise in this cohort.
- Define gene-environment interactions in female-predominant disorders such as autoimmune disease, if enough cases are found in this cohort.

6.0 Community Needs *and* Emerging Health Issues

GOAL: ***Ensure that the NIEHS and its research remains responsive to community needs and to newly emerging environmental health problems.***

Environmental health problems are dynamic and changing, frequently local in nature and often unexpected. Thus, NIEHS needs to be able to both assess and address local and regional concerns and have the flexibility and ingenuity to accommodate new research projects.

NEW OR EXPANDED OPPORTUNITIES

6.1 NATIONAL TOWN MEETINGS

Town meetings provide a regional public forum for local residents to share their environmental health concerns with the Director, NIEHS and his staff. These are generally full-day meetings preceded by an evening session that allows people who work to attend and state their concerns. Topics cover local issues such as urban sprawl (New Jersey) and water/air/soil pollution concerns (Tennessee), as well as broader health issues, such as asthma. NIEHS holds at least four town meetings each year. Input from these meetings helps to fashion both the research and the communication programs of the NIEHS.

Objectives:

- Provide American public with access to the Director, NIEHS.
- Offer the American public a convenient forum through which to influence the priorities of the Institute.

6.2 COMMUNITY OUTREACH AND EDUCATION PROGRAMS OF THE ENVIRONMENTAL HEALTH SCIENCE CENTERS

NIEHS requires that all its Centers develop and maintain community outreach and education programs (COEP). The objective of COEP is to address regional public health issues through the research facilities of the Centers. Among the possible activities included in this responsibility are:

- Continuing professional education;
- Disease prevention programs;
- Education at the primary, secondary, and/or college levels;
- Information dissemination;
- Community issue programs or public awareness seminars.

As a part of this effort, each NIEHS Center defines the community and region that it serves and develops outreach efforts specifically designed to address environmental health issues and problems of greatest concern to that community. Particular emphasis is given to populations that may be more susceptible to environmental insults, e.g., children, the elderly, or socioeconomically disadvantaged communities. NIEHS Centers are encouraged to sponsor local efforts through community organizations and to collaborate with other existing outreach programs in their area, such as those supported by other Federal agencies and state or local agencies or health departments. The performance of a Center's COEP is a critical component in the Institute's evaluation of that Center for continued funding.

Objective:

- Ensure that NIEHS-supported Centers are responsive to community needs by requiring a Community Outreach and Education Program (COEP) that emphasizes community involvement and that forms a critical evaluation component for continued NIEHS funding.

6.3 CENTER FOR EVALUATION OF RISKS TO HUMAN REPRODUCTION

There is widespread concern among the public that certain chemicals in the environment may have harmful reproductive and developmental effects. To address this concern, the NIEHS, under the auspices of the NTP, has established a unique center through which the public can nominate individual chemicals, or classes of chemicals, for the Institute to assess for their potential effects on reproduction and development. These assessments are made by panels of independent scientists who review all relevant information about a chemical, evaluate its probable effect on reproduction and development, and identify areas where more research and testing is needed. Panel meetings are open to the public and permit public comment. Final evaluations are provided as formal reports.

The first scheduled review is on seven phthalate compounds for which there are extensive exposures. Phthalates are commercial plasticizers used in products such as soft squeeze toys, medical tubing, balls, raincoats, and shower curtains.

Objective:

- Provide to the American people a forum for the expert evaluation of current literature on the reproductive and developmental effects of compounds of concern to them.

NIEHS *Retrospective*

COMMUNITY OUTREACH AT AN NIEHS-SUPPORTED CENTER

The NIEHS requires that each of its Centers around the country have a Community Outreach and Education Program (COEP) that is relevant to local needs. An excellent example of the value of this program can be found in California. The State of California requires routine assays in farmworkers of blood levels of acetylcholinesterase, an enzyme that serves as a biomarker of exposure to the major pesticides used in California agriculture. As part of its outreach responsibilities, the NIEHS Center at the University of California-Davis examined this monitoring program and discovered some surprising results. The commercial bioassays being used were inaccurate, often underestimating enzyme levels (and thus exposure effects) by as much as 40 percent. Furthermore the various assays available used completely different units of measurement, making meaningful comparisons difficult and cumbersome. The result was an extensive statewide monitoring program that could not provide accurate or useful information.

Photo Courtesy of News and Observer

As a result of these findings, the state's California Environmental Protection Agency rewrote its Public Worker Safety Regulations. It now requires standardized procedures for clinical laboratories for assessment of acetylcholinesterase activity in agricultural workers exposed to organophosphate and carbamate insecticides. Thus the practice of the law is now in line with the public health intent of the law. Such would not have been possible, however, without the work done by the UC-Davis COEP, and their subsequent followup with state regulators.

6.4 PHOTOTOXICITY CENTER

There is a substantial market today for cosmetic products and services, especially ones that claim to rejuvenate the skin. One such service is dermal peeling, which is performed to create a smoother, more youthful appearance. There is little information, however, on how dermal peels and other agents might combine with ultraviolet light (UV) exposures from the sun or tanning beds in a way that increases the known phototoxicity and photocarcinogenicity of UV radiation. The potential scope of this problem is unknown, in part because of a lack of suitable research facilities to generate that data. To address this situation, the FDA and the NIEHS, under the auspices of the NTP, have formed a Phototoxicity Center. This center will conduct rodent studies to assess a broad range of cosmetic chemicals and additives, sun block additives, tanning enhancers, skin colorants, and tattoo inks.

This Center will evaluate these compounds for their ability to increase an individual's susceptibility to sunburn, enhance development of skin cancers, and depress the immune system. The Center will also seek to understand how drugs or drug combinations interact with, and potentiate, sunlight and other UV exposures. This information can be used both to protect consumers and to enable industry to develop cosmetic formulations that do not have phototoxic side effects.

Objective:

- Protect consumers by evaluating how common cosmetic formulations, in the presence of UV radiation from sunlight or tanning booths, can enhance an individual's susceptibility to sunburn, skin cancer, and immune suppression (a partnership with FDA).

7.0 Career Development

GOAL: ***Ensure a well-trained workforce in the environmental health sciences that reflects the diversity of the American people.***

An important part of the NIEHS mission is to develop the next generation of young scientists and health care professionals who are committed to understanding the impact of environmental exposures on human health. Because many of these exposures occur among minority and disadvantaged populations, it is also important that the Institute take extra measures to recruit into environmental health science careers those individuals with ties to minority populations. These individuals will have credibility among these community members and can be expected to be particularly sensitive to their concerns regarding environmental health.

NEW OR EXPANDED OPPORTUNITIES

7.1 PHYSICIAN AND NURSE TRAINING

Physicians and nurses are at the front line of health care. For this reason they are ideally positioned to identify and remedy environmental health problems. Unfortunately there is little environmental health training in medical schools, and a lag in recruiting medical personnel into environmental health careers. The NIEHS has several programs that are aimed at improving the medical community's awareness of, and activity in, environmental health sciences.

Objectives:

- Develop environmental health sciences curricula appropriate for use in training physicians and nurses.
- Support mentorships that develop research scientists in the field of molecular epidemiology as it is applied to environmental health issues.
- Develop mentorships that train and encourage new investigators to pursue patient-oriented environmental health research.
- Increase the pool of physicians engaged in environmental health aspects of children's health (a partnership with EPA).
- Increase the pool of physicians engaged in identifying the environmental components of Parkinson's Disease (a partnership with NINDS).

7.2 MINORITY TRAINING AND SUPPORT OF MINORITY-BASED INSTITUTIONS

Minority, low-income, and disadvantaged populations are at greater risk of exposure to adverse occupational and other environmental agents. Moreover, these groups are often the least informed about environmental health risks and least able to use the political system to initiate change. For this reason, NIEHS is increasing recruitment of minority students into the environmental health sciences. This recruitment process should begin long before graduate school and need not be limited to traditional higher education. These efforts will help NIEHS develop a

NIEHS IS ACTIVELY RECRUITING MINORITY STUDENTS INTO ENVIRONMENTAL HEALTH SCIENCE CAREERS.

cadre of scientists with special ties to, and understanding of, affected communities.

Objectives:

- Recruit more African-Americans, Hispanics, Native Americans, and Pacific Islanders into biomedical research through a Minority Supplement Program that targets minority high school students, undergraduate students, graduate research assistants, postdoctoral students, and research faculty.
- Enhance the infrastructure of minority-predominant institutions through novel "bridge" or partnership grants between minority-predominant colleges and universities and larger, more resource-rich universities.
- Recruit and train into the field of remediation and environmental health those people who live in communities at risk of exposure from contaminated properties such as hazardous waste sites. This Minority Worker Training Program has the dual benefit of providing training and job skills for minority, inner-city youth and providing the community with a cadre of citizens with the skill and knowledge to identify environmental health problems (a partnership with EPA).

7.3 CAREER TRANSITIONS

Successful recruitment of environmental health scientists requires an awareness of the numerous transition points in a career where people can fail or where extra support could help ensure a continued career path. For example the transition between postdoctoral researcher and independent investigator is difficult and is a point where good investigators can become discouraged and drop their research ambitions. The NIEHS has taken special care to identify these critical career transition points and to develop programs that can ensure that talented scientists make the transition to full-time independent investigators.

Objectives:

- Ensure that exceptionally talented postdoctoral students can successfully transition into independent environmental health research positions. The Institute has initiated a grant program, Transition to Independent Positions (TIP), in which funding is transferable to any research institution to which young postdoctoral students move as they undergo the transition from postdoctoral research to independent investigator research.
- Develop 3-, 4-, and 5-year formal mentorships that recruit clinician researchers into the field of environmental health sciences.
- Encourage midcareer transitions into patient-oriented environmental health research by supporting successful clinicians to more fully explore these research opportunities and to mentor young clinicians in the field.

8.0 Communication

GOAL: ***Enhance the understanding of environmental health sciences and its importance to human health among scientists, policy makers, and the American public.***

This understanding will increase the ability of this nation to make wise environmental health choices and improve the understanding of environmental public policy decisions aimed at protecting health.

NEW OR EXPANDED OPPORTUNITIES

8.1 COMMUNICATING TO THE SCIENTIFIC COMMUNITY

The substantial increase in our understanding of how environmental triggers affect human health make it imperative that the entire scientific community be aware of this information. This interdisciplinary contact will help generate further research in other fields of health complementary to NIEHS work.

Objectives:

- Increase circulation of the NIEHS journal, *Environmental Health Perspectives*.
- Develop communication documents targeted to specific areas of research where greater scientific effort needs to be focused on environmental aspects of disease.
- Increase the NIEHS presence at national conferences and workshops so that the scientific community can be made aware of funding and research opportunities at the NIEHS.

8.2 COMMUNICATING TO THE GENERAL PUBLIC

The diversity of the American public requires a versatile approach to communicating the various types of environmental health information appropriate to their individual needs. Therefore, NIEHS is planning to use different communications tactics to reach and educate the diverse groups that make up the American public.

Objectives:

- Produce public health messages about important issues such as ozone, lead, and water quality. The target audience for these messages would be children, teens, parents, and teachers.
- Evaluate the current NIEHS and NTP websites and make any changes needed to ensure that they are user-friendly, accessible, and responsive to the needs of the American public.
- Explore non-print communication avenues such as a Speaker's Bureau of intramural scientists or use of a celebrity spokesperson.

8.3 COMMUNICATING TO SPANISH-SPEAKING AND MINORITY COMMUNITIES

The NIEHS message needs to be accessible to all Americans; but the growing community of Spanish-speaking and Asian citizens makes it imperative to expedite special communication tools for these groups, as well as to African-Americans.

THE INSTITUTE'S JOURNAL, *ENVIRONMENTAL HEALTH PERSPECTIVES*, SERVES AS A MAJOR COMMUNICATION TOOL TO BOTH SCIENTISTS AND THE PUBLIC.

Objectives:

- Increase the number of informative booklets and pamphlets that are translated into Spanish.
- Ensure that press releases target specific outlets such as the West Coast Asian press and African-American publications.
- Develop more news material, such as that from *Environmental Health Perspectives*, into a Spanish language format.

8.4 COMMUNICATING BASIC ENVIRONMENTAL SCIENCE TO YOUNG STUDENTS

Over the next decade, the environment will be an increasingly important part of public health policy. An educated public will be the best advocates for the changes needed to collectively improve our environmental health. To enhance the understanding of environmental health sciences in tomorrow's adults, booklets are needed that explain important environmental health initiatives in terms that today's teenage audience can understand and relate to. Initial booklets will focus on Gene-Environment Interactions and Alternative Methods of Testing.

Another benefit of this effort will be to encourage students to explore careers in science. To enhance the recruitment of under-represented minorities into tomorrow's cadre of scientists, special efforts will be made to reach out to these communities. NIEHS will produce Public Service Announcements, in both Spanish and English that encourage mentoring of students. These videos will show minority children in different situations growing up to be scientists, doctors, and teachers.

Objectives:

- Develop a booklet targeted to children that explains gene-environment interactions.
- Develop a booklet targeted to children that outlines the importance of toxicological testing and the new alternative methods being developed.
- Review the KidsPage on the NIEHS website to ensure that it is maximally effective in educating children about environmental health sciences in ways that are engaging and fun.
- Extend the distribution of the NIEHS booklet, "Environmental Diseases from A to Z," among teachers, students, and Parent Teacher Associations.

9.0 Management

GOAL: ***Ensure responsible stewardship of the NIEHS research enterprise.***

As a publicly-funded research enterprise, the NIEHS is obligated to support the best programs in the most cost-effective manner. Toward that end, the Institute has a number of initiatives aimed at reviewing existing programs, determining if they meet their goals, and assessing if they represent the best investment by the Institute.

NEW OR EXPANDED OPPORTUNITIES

9.1 PROGRAM EVALUATIONS BY EXTERNAL GROUPS

Although there is regular oversite of NIEHS programs through the National Environmental Sciences Advisory Council, the Institute has also found it useful to periodically convene groups of outside experts to evaluate specific components of the NIEHS. In 1994, overall management of the NTP was evaluated, and in 1996, the process used to produce the *Report on Carcinogens* was reassessed and modified. In 1998 the DIR Epidemiology Branch was evaluated, as was the overall NIEHS enterprise and responsiveness to its partners' needs in 1999. Currently, the training program that recruits students into environmental science careers is being evaluated. In 2000, the entire extramural research program will be evaluated for its productivity and quality; and in 2001, the management of the NIEHS intramural research endeavor will be critiqued.

Objectives:

- Ensure that NIEHS scientific programs are supporting the best science possible.
- Ensure that NIEHS training programs are providing the numbers of environmental health scientists needed to fulfill the public's need for research in this area.
- Ensure that NIEHS is benefiting from the best possible management of its intramural programs.
- Ensure that NIEHS is using cutting-edge technologies to exploit the best scientific opportunities.

9.2 PROPERTY MANAGEMENT

The American people provide NIEHS financial resources to purchase equipment and supplies to fulfill its research mission. It is incumbent upon the Institute to ensure that this property is carefully inventoried and tracked. The NIEHS has determined that the current system is cumbersome and insufficiently responsive to such tracking. Therefore, the Institute is currently conducting both in-house and contractor studies of all property management processes. This will include process streamlining and automation needs, identification of system functional requirements, evaluations of existing products that could be applied to our purposes, Property Management Information System (PMIS) reconciliation capabilities, web-based property forms and handbooks, and education and training of custodians, ordering, and receiving officials to enable them to more productively and effectively handle property management responsibilities.

Objectives:

- Ensure timely, responsive, and cost-effective management of equipment and supply purchases, inventory, and maintenance.
- Identify, acquire, and implement an automated "tracking system" for NIEHS that will facilitate record keeping and simplify property management processes for all new property acquisitions.
- Develop web-based automated property forms and tracking processes that expedite and simplify record-keeping for property to be moved, transferred, returned for credit against new acquisitions, made available as surplus, or disposed of by any other means.
- Update the NIEHS Property website to include a user-friendly handbook for property custodians, ordering officials, and users seeking information on proper procedures for various actions.
- Provide an automated means of updating information in the NIH Property Management System (PMIS) to reflect custodian changes, new room assignments, employee transfers, supervisory changes, etc., to ensure that property tracking information remains accurate at all times.

9.3 HEALTH AND SAFETY REVIEWS

The NIEHS Health and Safety Branch will develop a plan to evaluate Institute programs in the areas of employee health, safety and environmental compliance. This plan will integrate various approaches for program evaluation including self-audits, benchmarking comparisons with other biomedical research organizations, employee and supervisor surveys/interviews, and evaluation by external entities. The Institute is already subject to external inspections and reviews on radiation safety (by NRC), employee health and safety in our animal care programs (by AAALAC), hazardous waste management and air emissions (by State regulatory officials), fire safety (by Durham Co. Fire Marshal), and wastewater discharges (by Durham Co.). There are also various reports mandated by regulatory authorities that can provide additional measures of program performance (e.g., annual OSHA injury and illness log). The health and safety program evaluation plan would include these existing processes along with other areas for consideration (e.g., employee training and information, biological safety, occupational health and wellness, contractor safety oversight, etc.).

Objectives:

- Ensure that NIEHS health and safety programs provide appropriate levels of risk management, consistent with current regulatory requirements and current understanding of potential hazards and exposures associated with new or developing research technologies.
- Provide an integrated plan for the external evaluation of NIEHS health and safety programs.
- Identify best practices that could be implemented to enhance current programs and services.

NIEHS

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